

Short Report

Discontinuation and nonpublication of interventional clinical trials conducted in patients with mild cognitive impairment and Alzheimer's disease

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Abstract

Introduction: Discontinuation and nonpublication of interventional clinical trials represents a waste of already scarce resources. We sought to identify the prevalence of discontinuation and nonpublication of interventional clinical trials conducted in patients afflicted by mild cognitive impairment and Alzheimer's disease.

Methods: We conducted a retrospective, cross-sectional study on mild cognitive impairment and Alzheimer's disease–based interventional clinical trials in ClinicalTrials.gov dating back to 1995. The analyzed data included trial phase, intervention type, enrollment, and funding sources. Fisher's exact and χ^2 tests were used to determine any potential associations between trial characteristics and completion.

Results: A total of 744 studies were identified, of which 502 (67%) were industry-sponsored ones. A total of 127 (17%) were discontinued prematurely. Of the 617 completed trials, 450 (73%) were not published, representing approximately 66,655 participants who incurred the risks of trial participation without subsequently contributing to the medical literature. Similarly, there were 18,246 patients from unpublished, discontinued trials. Of the 744 trials examined, 247 publications from 167 trials could be identified via PubMed/MEDLINE and EMBASE searches. Most notably, the odds of nonpublication among industry-sponsored trials were more than 75% higher than those in studies funded by academia (odds ratio = 1.78; 95% confidence interval, 1.14–2.78; $P = .01$). Furthermore, industry-sponsored trials had a 50% greater odds of study discontinuation compared with trials funded by academia (odds ratio = 1.50; 95% confidence interval, 1.04–2.16; $P = .03$).

Discussion: The nonpublication of many trials and preliminary results of trials that are discontinued early dilutes the quality and decreases the comprehensive nature of the medical literature. This occurs in both industry and academia. Publication of inconclusive or negative results ensures that all research activities, regardless of outcome, contribute to global medical knowledge.

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Keywords:

Clinical trials; Discontinuation; Nonpublication; Mild cognitive impairment; Alzheimer's disease

1. Introduction

Discontinuation of interventional clinical trials and nonpublication of completed trials represent a waste of already scarce resources. This waste relates to all types

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of research occurring at multiple stages of the production of medical evidence, including the underreporting of trial methods and results [1,2]. There is evidence that trials with positive findings are published more often and more quickly than trials with negative findings [3]. Furthermore, citation bias has been shown to lead to an overrepresentation of positive results [4]. Academic researchers may not wish to invest the time and effort to publish studies that might yield negative outcomes. Academic competition and pressure have been shown to increase the risk of scientists' bias in not publishing negative studies [5]. Industry sponsors may be cautious to publish results which might reveal current or lack of progress of their research to competitors. Nevertheless, the nonpublication of trial findings undermines the available medical evidence by misrepresenting the apparent safety and efficacy of interventions and compromises clinical guidelines and evidence-based clinical practices [6–8]. This is of particular importance in the field of mild cognitive impairment (MCI) and Alzheimer's disease (AD) research, considering the many disappointing trials with high costs and lack of a successful drug after decades of research in addition to the urgent need of a therapy, given the aging world population, among others. The aim of this study was to identify the prevalence of discontinuation and nonpublication of interventional clinical trials conducted in MCI and AD patients.

2. Methods

We conducted a retrospective, cross-sectional search of MCI- and AD-based interventional clinical trials in ClinicalTrials.gov dating back to 1995. This search was limited to trials in humans and to studies listed as “completed,” “terminated,” “withdrawn,” or “suspended.” Data were collected from the registry, and associated publications were identified (final search was performed on January 15, 2018). We included interventional clinical trials that were not active, recruiting, or enrolling and for which recruitment status was known. Trials were considered published if they were linked with a national clinical trial identifier number. Details of analyzed trials provided data on the funding sources (industry or academia), intervention type, trial phase, and enrollment numbers (Table 1). Fisher's exact and χ^2 tests were used to determine any potential associations between trial characteristics and trial completion. Reasons for trial discontinuation were tabulated based on data provided in ClinicalTrials.gov entries.

We opted not to contact the trialists because we wanted to represent the amount of information and level of detail that is accessible to the average clinician searching the literature. Although we recognize that unpublished results can at times be obtained by reaching out to investigators, we felt that doing so would dilute the potential publication bias that we sought to evaluate.

Table 1
Characteristics of completed and discontinued trials

	Completed trials (n = 617), n (%)	Discontinued trials (n = 127), n (%)	All trials (n = 744), n (%)	P
Clinical trial characteristics				
Primary funding source				.01*
Academic institution	213 (35)	29 (23)	242 (33)	
Industry	404 (65)	98 (77)	502 (67)	
Intervention				.07†
Drug	476 (77)	110 (87)	586 (79)	
Other	54 (9)	8 (6)	62 (8)	
Behavioral	50 (8)	3 (2)	53 (7)	
Device/procedure	37 (6)	6 (5)	43 (6)	
Trial phase‡				.06*
Phase 1	125 (20)	23 (18)	148 (20)	
Phase 2	201 (33)	41 (32)	242 (33)	
Phase 3	119 (19)	38 (30)	157 (21)	
Phase 4	61 (10)	11 (9)	72 (10)	
Unknown	111 (18)	14 (11)	125 (17)	
Enrollment				<.0001†
<50	231 (37)	64 (50)	295 (40)	
50–100	118 (19)	16 (13)	134 (18)	
101–250	126 (20)	16 (13)	142 (19)	
>250	126 (20)	30 (24)	156 (21)	
Unknown	16 (3)	1 (1)	17 (2)	

*Determined using χ^2 test.

†Determined using Fisher's exact test.

‡Trials described as phase 1/2 (n = 19) were categorized as phase 2, and trials described as phase 2/3 (n = 15) were categorized as phase 3.

3. Results

Seven hundred forty-four trials met our inclusion criteria, from which a total of 247 publications from 167 trials could be identified via PubMed/MEDLINE and EMBASE searches. The included trials employed strategies such as novel drugs (n = 586; 79%), other (such as cognitive training and exercise programs) (n = 62; 8%), behavioral interventions (n = 53; 7%), and devices/procedures (n = 43; 6%). Fifty-four percent of trials were performed in either phase 2 or 3 settings. Between 2007 and 2016, there were approximately two and half times as many trials as those in the previous decade. A total of 744 studies were identified, of which 502 (67%) were industry-sponsored ones. A total of 127 (17%) were discontinued prematurely whereby 111 were terminated. Of the 617 completed trials, 450 (73%) were not published, representing approximately 66,655 participants who incurred the risks of trial participation without subsequently contributing to the medical literature. Similarly, there were 18,246 patients from unpublished, discontinued trials. Only 19% (n = 86) of unpublished trials posted results on ClinicalTrials.gov. Over 65% of the reasons for trial discontinuation were due to unspecified/unclear reasons or informative termination (changes in standard of care and safety or efficacy findings) (Table 2).

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